Third Quarterly Progress Report

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Neurophysiology Studies of Stimulated Auditory Prostheses

Claus-Peter Richter

Northwestern University
Feinberg School of Medicine
303 E. Chicago Ave

Chicago, IL 60611-3008
cri529@northwestern.edu

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Introduction

Neural prosthetic devices are artificial extensions to the body that restore or supplement nervous system function that was lost during disease or injury. Particular success has been realized in cochlear prostheses development. The devices bypass damaged hair cells in the auditory system by direct electrical stimulation of the auditory nerve. Stimulating discrete spiral ganglion cell populations in cochlear implant users' ears is similar to the encoding of small acoustic frequency bands in a normal-hearing person's ear. In contemporary cochlear implants, however, the injected electric current is spread widely along the scala tympani and across turns. Consequently, stimulation of spatially discrete spiral ganglion cell populations is difficult. One goal of implant device development is to design cochlear implants that stimulate smaller populations of spiral ganglion cells. In contrast to electrical stimulation, extreme spatially selective stimulation is possible using light.[1-5] Therefore, the goal is to develop and build optical cochlear implant prostheses to stimulate small populations of spiral ganglion cells. Steps towards this objective include (1) quantify the optical parameters that allow for safe spiral ganglion cell stimulation over extended periods of time, (2) characterize the fundamental spatial and temporal properties of optical stimulation of the auditory nerve, (3) determine the spatial resolution for laser stimulation. By accomplishing the first three goals within the first three years, we will be able (4) to build and implant the first animal cochlear implant electrode for long-term safety studies during years four and five. Also, the results will provide a basic set of parameters that can be used for other neural interfaces that use optical radiation to stimulate neurons.

During the third quarter we continued working on Step I: Quantify the parameters that allow the safe use of laser radiation for auditory nerve stimulation. The objectives for Step I include acute experiments in normal hearing and in long-term deafened gerbils. An optical fiber is placed after surgical access to the cochlea close to the modiolus. The optical fiber is coupled to a radiation source. While the auditory system is stimulated with optical pulses, compound action potentials are recorded at the round window for different stimulus parameters: radiation wavelength, pulse length, pulse repetition rate, increasing optical energy, extended stimulation times, different diameters of the optical fiber between 50 and 600 μm, variable fiber distances and orientations from the spiral ganglion cells in the modiolus, and for different locations of optical fiber placement along the cochlea. Measuring the peak-to-peak amplitude of the optically evoked potential serves to monitor cochlear function. The CAP amplitude decreases when cochlear damage occurs. The results provide the safe stimulation parameters for optical stimulation of the auditory system.

Summary of activities from May 1, 2007 to July 31, 2007:

Personnel involved

Paid by the grant

Izzo, A.: post-doctoral student
Otting, M.: Technician
Eul, Suh: Technician
Richter, C.-P.: PI

Part of their training

Littlefield, P.: Neurotology Fellow
Nevel, A.: pre-medical student
Bradley, A.: Student at the Department of Biomedical Engineering
Hotaling, Jeffrey: medical student (summer research)
Goyal, Sheila: medical student (summer research)

In June, 2007, Maragrete Otting resigned from her position as technician following her husband who matched for a residency position in Pittsburg. Eul Suh has filled the open position. She has been working in the laboratory since 2004.

Technical activities

We further tested multi-channel recording system from Plexon using artificial data. The system has not been used for animal experiments in guinea pigs.

Current problems relate to different factors:

1.) Anesthesia: It is becoming increasingly difficult to obtain the veterinarian grade anesthetic, Nembutal. The price per 50 ml bottle increased from ~$40 per bottle to ~$400 per bottle. To maintain the cost for anesthetics reasonable we used a mixture of Ketamine/Xylazine for anesthesia. While Ketamin/Xylazine are ideal to maintain a good level of anesthesia during data acquisition, the anesthetic appeared not ideal for surgery. The level of anesthesia is not sufficient for surgery and lidocaine was used locally. The veterinarians were contacted to improve the anesthetic regime. They suggested using an inhalation anesthetic, rather a mixture of Ketamine/Xylazine. I am currently in the process to determine, which anesthesia system is suitable to ventilate guinea pig and cats.

2.) The surgical access for placing the optical fiber in guinea pigs had to be adjusted from previous experiments, which were made in gerbils.

We attended the conference on implantable auditory devices July 15 – July 20, 2007. During the meeting the results of our experiments were presented in a podium presentation and in one poster. Important feedback has been gained through subsequent discussions.

<u>Tone-on-light masking</u>

Our hypothesis is that light can provide a more spatially selective stimulation of the cochlea than electric current. Spatial selectivity has been measured with a masking method. Tone-on-tone masking experiments have been used for decades as a means of assessing the frequency selectivity of cochlear responses to a probe tone. Here, the probe tone has been replaced with a probe pulse of light and the cochlear response to the light pulse has been masked with an acoustic masker, tone-on-light masking. Results from tone-on-light masking in gerbils reveal tuning curves with best frequencies between 6 – 11 kHz. Sharpness of tuning (Q_{10dB} ratios) were between 2 and 7. The results from the tone-on-light tuning curves were similar to tone-on-tone and single fiber tuning curves measured from gerbils. In addition, tone-on-electric masking experiments were conducted. It was not possible to mask the probe (electric current) evoked response with any acoustic masker. From these results, we conclude that optical stimulation of the cochlea can provide much more localized stimulation than electric current. The experiments have been completed and a manuscript is in preparation.

<u>The effect of a wavelength with short penetration depth in water</u>

Very little of the available optical parameter space has been used for optical stimulation of neurons. Here, we used a pulsed diode laser (1.94 µm) to stimulate auditory neurons of the gerbil. Radiant exposures measured at CAP threshold are similar for pulse durations of 5, 10, 30, and 100 µs, but greater for 300-µs-long pulses. There is evidence that water absorption of optical radiation is a significant factor in optical stimulation. Heat-transfer-based analysis of the data indicates that potential structures involved in optical stimulation of cochlear neurons have a dimension on the order of ~5 µm. The experiments have been completed, a manuscript has been written and submitted to the Biophysical Journal.

<u>Acutely and chronically deafened animals</u>

The correlation has been measured between surviving spiral ganglion cells after acute and chronic deafening with neomycin application into the middle ear and neural stimulation with optical radiation and electrical current. *In vivo* experiments were conducted in gerbils. Pre-deafening acoustic thresholds were obtained and stimulation with optical radiation was made at various pulse durations, energy levels and repetition rates. In one group of animals, measurements were made immediately after deafening, while the other group was tested after chronic deafening. Deafness was confirmed by measuring acoustically stimulated compound action potentials. Optically and electrically evoked compound action potentials and auditory brainstem responses were determined for different radiation exposures. After completion of the experiments, the animals were euthanized and the cochleae were harvested for histology. For acute deafening procedures, thresholds for acoustic compound action potentials were significantly elevated after neomycin application. Thresholds for optical radiation were affected minimally. For chronic deafening experiments that allowed neural degeneration to occur, the thresholds and amplitudes of the compound action potential depended on the number of surviving spiral ganglion cells.

The results have been presented in part at the CIAP at Tahoe, July, 2007. A manuscript is in preparation for submission in Hearing Research.

<u>Scatter of the radiation</u>

Interaction of the laser radiation with the tissue determines the spatial distribution of light in the tissue and fall into two broad categories: absorption and scattering. Both are highly dependent on the wavelength of the light and the tissue characteristics. To a first approximation, absorption dominates the light-tissue interaction in the mid-infrared wavelength range. The axial distribution of a primarily absorbed wavelength can be determined using Beer's Law, a description of the exponential decrease of laser energy over the optical path. However, scattering does play some small role in the light-tissue interaction at mid-infrared wavelengths. Spatial scatter is caused by random spatial variations in tissue density, refractive index, and dielectric constant. While it has been reported that the scattering decreases monotonically with wavelength, a rigorous description of the multiple scattering events that occur as a collimated beam propagate through tissue is extremely difficult. The full-width half-maximum (FWHM) of the radiation beam has been determined to quantify the effect of different tissues on the beam width. Tissues included skin, muscle tissue, fatty tissue, bone in general, pig temporal bones, pig bones from the modiolus, human temporal bones, and bone samples from the modiolus of human cochleae.

The spread of the optical beam due to air was found to be negligible. Lactated ringer's solution caused the beam to spread at an average angle of 3.14°±0.86. Pig temporal bone resulted in an average spread angle of 19.46°±2.54. Rat muscle produced an average spread angle of 13.23°±3.57. Human cochlear bone produced an average spread angle of 13.24°±4.95. The sample dimension that caused a 1/e attenuation of laser energy for Lactated Ringer's solution was

1.15 mm, for muscle 0.9 mm, for skin 0.37 mm, and for fat 0.80 mm. Cochlear bone and temporal bone attenuated the energy to 1/e at 0.70 mm and 0.26 mm respectively. The measurements have been completed and a manuscript is in preparation for publication in JBO.

Activities for the fourth quarter

1. Continue analyzing the data and prepare the single fiber data for publication
2. Publish the data obtained in acutely and chronically deafened animals and complete control experiments if necessary
3. Confirm results from the gerbils in guinea pigs
4. Test the multi-channel system by recording from the guinea pig inferior colliculus.
5. Complete the manuscript on the study on the effect of tissue on the beam profile.

Publications resulting from the activities (September 2006-July 2007) copies of the new manuscripts are enclosed and posters are available on the internet. Publications during the last quarter are in blue)

<u>*Peer reviewed*</u>

1. Izzo, A.D., M. Bendett, M.E. Jansen, E., Jim Webb, Heather Ralph, Walsh, Jr., J.T., Richter, C.-P. (2007) Optical Parameter Variability in Laser Nerve Stimulation: a study of pulse duration, repetition rate, and wavelength. IEEE 54 (6), 1108-1114.
2. Teudt, I.U., Nevel, A., Izzo, A.D., Walsh, Jr., J.T., Richter, C.-P. (2007) Optical stimulation of the facial nerve – a new monitoring technique? The Laryngoscope (in press).
3. Izzo,A.D., Joseph T. Walsh, Jr., J.T., Ralph, H., Webb, J., Bendett, M., Wells, D., Richter, C.-P. (2007) Laser stimulation of auditory neurons: Effect of pulse duration and penetration depth. Biophys J. (in review).

<u>*Proceeding paper*</u>

1. Izzo A.D., Littlefield, P., Walsh, Jr., J.T., Webb, J., Ralph, H., Bendett, M., Jansend, D.E. and Richter, C.-P. (2007) Laser stimulation of auditory neurons at high repetition rate, SPIE Vol. 6435, 64350R-1 - 64350R-7.

<u>*Abstracts*</u>

1. Suh, E., Agnella D. Izzo, A.D., Walsh Jr., J.T., Richter, C.-P. (2007) The role of Transient Receptor Potential channels in neural activation. Abstr. Assoc. Res. Otolaryngol. 30, 109.
2. Izzo, A.D. Lin, A., Oberoi, M., Walsh, Jr.[1], J.T., and Richter, C.-P. (2007) Tone-on-light masking reveals spatial selectivity of optical stimulation in the gerbil cochlea. Abstr. Assoc. Res. Otolaryngol. 30, 446.
3. Littlefield , L., Izzo, A.D, Mundi, J., Walsh, Jr., J.T., Jansen, D.E., Bendett, M., Webb, J. Ralp, H., Richter, C.-P. (2007) Laser stimulation of the auditory nerve stimulation is possible at high repetition rates. Abstr. Assoc. Res. Otolaryngol. 30, 356.
4. Bayon, R., Otting, M., Izzo, A.D., Walsh Jr., J.T., Richter, C.-P. (2007) Optical stimulation of the auditory nerve before and after deafening in adult gerbils. CLO, April 9, Chicago

5. Bayon, R., Otting, M., Izzo, A.D., Walsh Jr., J.T., Richter, C.-P. (2007) Laser stimulation of the auditory nerve before and after acute deafening in adult gerbils. Meeting of the AAO-HNS, Sept 2007.
6. Walsh, Jr., J.T., Izzo, A.D., Richter, C.-P. (2007) Optical Stimulation of Neural Tissue: Results from the Auditory System.
7. Richter, C.-P., Rodrigo, Bayon, R., Philip Littlefield, P., Izzo, A.D., Joseph T. Walsh Jr., J.T. (2007) Stimulation of the auditory nerve using optical radiation. CIAP
8. Izzo, A.D., Ralph, H., Webb, J., Wells, J., Bendett, M., Walsh, Jr., J.T., E. Jansen, D., Richter, C.-P. (2007) Laser stimulation of the auditory system: selectivity and optical parameters. CIAP

References

1. Wells JD, Kao C, Mariappan K et al. Optical stimulation of neural tissue in vivo. *Optics Letters* 2005;30:504-506.
2. Richter C-P, Izzo AD, Walsh Jr. JT, Jansen DE. Optical Stimulation of the Auditory System. *Neural Interface Workshop, NIH, Bethesda* 2005.
3. Richter C-P, Izzo A, Walsh J, Jansen DE. Spatial cochlear tuning obtained with optical stimuli. *Conference on Implantable Auditory Prostheses Asilomar* 2005.
4. Izzo A, Richter C-P, Walsh J, Jansen D. Safe ranges for optical cochlear neurons stimulation. *Abstr Assoc Res Otolaryngol* 2005;28:1013.
5. Richter C-P, Izzo A, Walsh J, Jansen D. Optically-evoked Acoustic Nerve Activity. *Abstr Assoc Res Otolaryngol* 2005;28:1012.
6. Welch AJ, van Gemert MJC. *Optical-Thermal Response of Laser-Irradiated Tissue.* New York: Plenum Press, 1995.